

Subtrochanteric Femoral Insufficiency Fracture Following Bisphosphonate Therapy for Osseous Metastases

Lisabeth A. Bush, M.D., and Felix S. Chew, M.D.

We present the case of an insufficiency fracture of the femoral shaft in a 61-year-old man who had received bisphosphonate therapy to reduce the fracture risk from lytic renal cell carcinoma metastases to the spine. Approximately 1.5 years after beginning monthly intravenous infusions of zoledronic acid (Zometa), the patient complained of persistent thigh pain. Radionuclide bone scan showed mildly increased activity in the lateral subtrochanteric cortex of the right femur, where there was focally increased T2 signal on MRI and a small, triangular ridge or cortical beak on radiographs. The lesion was initially thought to represent a metastasis, but after the patient returned with a transverse femoral shaft fracture through the ridge following minimal trauma, MRI and biopsy of the lesion failed to show any evidence of tumor. We suggest that this fracture is similar to the low-energy proximal femoral shaft fractures recently reported in postmenopausal women who have received oral bisphosphonates for osteoporosis. Suppression of bone turnover may play a role in the development of these fractures.

Introduction

Insufficiency fractures are by definition caused by a low-energy event, usually normal physiologic muscular activity which fractures bone that is abnormal in mineralization, elasticity, or ability to repair injury [1, 2]. Insufficiency fractures are distinguished from stress fractures, in which abnormal repetitive stress with inadequate time for recovery and repair of microscopic damage leads to fracture of otherwise normal bone. Tumor or infection may also abnormally weaken bone focally, leading to pathologic fracture from a minimal trauma or low-energy event. Insufficiency fractures are known to occur in conditions of abnormal bone mineralization, metabolism, and remodeling, such as Paget disease, osteomalacia or rickets, osteopetrosis, osteoporosis,

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Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

Lisabeth A. Bush, M.D. (Email: bush4msk@u.washington.edu), and Felix S. Chew, M.D., are in the Department of Radiology, University of Washington, Seattle, WA, USA.

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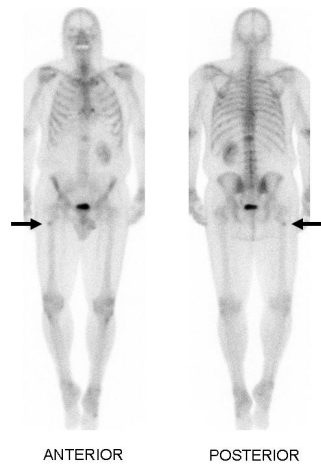


Figure 1. 62-year-old man on bisphosphonate therapy for osseous metastases. Tc99m-MDP anterior and posterior whole body bone scan demonstrates a subtle region of focal uptake at the lateral subtrochanteric aspect of the right femur (arrow). Additional findings include metastatic spine lesions and prior nephrectomy.

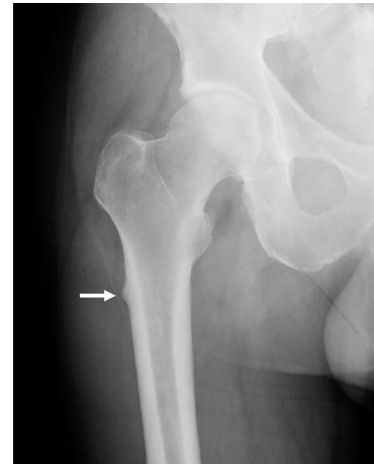


Figure 2. 62-year-old man on bisphosphonate therapy for osseous metastases. AP radiograph of the right femur with a 1 cm bony excrescence projecting from the lateral aspect of the femoral cortex in the subtrochanteric region (arrow), corresponding with the abnormality seen on radionuclide bone scan.

osteogenesis imperfect, rheumatoid arthritis, radiated bone, fluorosis, pyknodysostosis, fibrous dysplasia, hyperparathyroidism, metabolic bone disease, and renal osteodystrophy [1-6].

Due to the strength of the subtrochanteric region of the femur, between the lesser trochanter and the junction of the proximal and middle third of the femoral shaft, fractures in this region are usually related to high-energy trauma [5, 6], but rare cases of stress fractures in runners and athletes [8,9] and insufficiency fractures due to Paget disease, osteomalacia, pyknodysostosis, and fluorosis have been reported [3,5]. Insufficiency fractures in the subtrochanteric and middle third of the femur have recently been recognized in postmenopausal women receiving oral bisphosphonate therapy for osteoporosis [5, 6, 10-12]. Characteristic features have been described with these fractures and a mechanism proposed: inadequate osteoclast activity to allow normal remodeling and repair of normally occurring microscopic damage [5, 6, 10-12].

We present the case of an insufficiency fracture of the proximal femoral shaft in a 61-year-old man who was receiving intravenous bisphosphonate therapy to reduce the fracture risk of lytic spinal metastases from renal cell carcinoma. We suggest that this fracture is sim-

ilar to the insufficiency fractures of the proximal femoral shaft described with oral bisphosphonate therapy, and that abnormal bone remodeling underlies this and other conditions that lead to insufficiency fractures of the subtrochanteric femoral shaft. stones [6]. There is no left or right predominance [8]. The stones themselves are typically composed of calcium phosphate or calcium carbonate in association with other salts and organic material such as glycoproteins, desquamated cellular residue, and mucopolysaccharides. Bacterial elements have not been identified at the core of a sialolith [9]. Some factors inherent to the submandibular gland tend to favor stone formation there like longer and larger caliber duct, flow against gravity, slower flow rates and higher alkalinity along with higher mucin and calcium content of the saliva [10]. The submandibular gland hosts the largest stones with the largest reported one being 6cm in length [11]. Most submandibular stones are found in the salivary duct (75 to 85% of cases) [12]. Hilar stones tend to become very large before becoming symptomatic. Ductal stones are elongated in shape whereas hilar stones tend to be oval [13].



Figure 3. 62-year-old man on bisphosphonate therapy for osseous metastases. Pre-fracture MRI. Ultrafast gradient sequence following administration of gadolinium, performed to re-stage abdominal disease, yields a fortuitous glimpse of abnormally increased marrow signal at the level of the cortical ridge (arrow).



Figure 4. 62-year-old man on bisphosphonate therapy for osseous metastases. Subtrochanteric femur fracture which extends through the center of the cortical ridge seen on the prior radiographs. The distal component is posteromedially displaced and medially angulated.

Case Report

A 62-year-old man presented with right thigh pain. Past medical history was significant for renal cell carcinoma. Because of metastases to the spine, the patient had been receiving intravenously administered zoledronic acid (Zometa), a bisphosphonate medication for approximately 1.5 years. Because of concern for possible metastatic disease in the femur, diagnostic imaging was obtained. A Tc99m-MDP bone scan demonstrated mildly increased focal uptake in the lateral cortex of the subtrochanteric femoral shaft (Fig. 1). Subsequent radiographs of the right femur demonstrated mild, diffuse cortical thickening and a triangularly shaped focal ridge or beak projecting from the lateral cortex (Fig. 2). Due to the patient's underlying malignancy, concern was raised for a potential impending pathologic fracture. An MRI performed at this point for re-staging for disease in the abdomen and pelvis coincidentally included a glimpse of this portion of the femur on a single ultrafast gradient sequence after the administration of gadolinium contrast. The lateral cortex was slightly thickened and had a focus of abnormal high signal (Fig. 3), which was thought to be consistent with a metastatic deposit. The contralateral femur was normal in signal, however its diaphyseal cortex also appeared slightly thickened.

One month later, the patient slipped and twisted his leg in an awkward way while trying to catch his balance. While twisting, he felt his leg break, and then unable to bear weight, he fell to the floor. Radiographs of the fracture site showed a simple, transverse, subtrochanteric femoral shaft fracture that extended through the middle of the triangular cortical ridge seen on the earlier radiograph (Fig. 4). Due to persistent concern for metastasis, an MRI was obtained prior to operative fixation of the fracture. The MRI demonstrated marrow edema related to the fracture and hemorrhage in the surrounding soft tissues as would be expected following an acute fracture (Fig. 5), but no evidence of an enhancing mass lesion or tumor at the fracture site. The patient underwent surgical reduction and internal fixation with a Stryker gamma nail (Fig. 6). At the time of surgery, a curetted specimen of the bone was obtained. Histologic examination of this specimen confirmed the absence of metastatic disease. No osteoclasts were evident in any high power field (Fig. 8); a finding thought to be consistent with bisphosphonate therapy. Follow up radiographs of the fracture site showed exuberant fracture callus (Fig. 7).

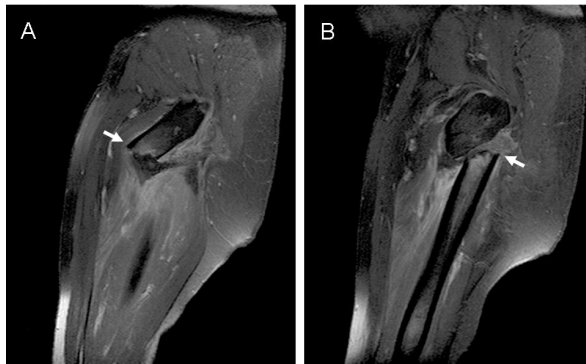


Figure 5. 62-year-old man on bisphosphonate therapy for osseous metastases. Subtrochanteric femur fracture MR images A-B. Increased T2 signal consistent with edema at the fracture site and slight cortical thickening at the lateral aspect of the fracture (arrow). No focal lesion or enhancement to suggest neoplasm.

Discussion

Because of its great strength in the healthy body, the subtrochanteric portion of the femoral shaft typically requires the application of considerable force to fracture. Its remodeling is stimulated as a center of maximal bending movement [6, 7]. If this remodeling is dysfunctional or inadequate to repair accumulating microscopic damage, this maximal center of bending force becomes a critical site for fracture and potentially life threatening fractures can be caused by low-energy mechanisms [6, 15].

Our patient experienced prodromal pain and had imaging studies with characteristic uptake on bone scan, abnormal signal on MRI, and formation of a ridge or beak at the site of impending fracture on a background of diffuse bilateral cortical thickening of the femoral diaphyses. He then incurred a subtrochanteric femoral fracture with a simple twisting motion of his femur. This low-energy mechanism of trauma is consistent with an insufficiency fracture and is likely related to inadequate remodeling response to accumulating damage as has been postulated by other authors [5, 6, 10-13]. The patients in other series were women taking oral forms of bisphosphonate medication, specifically alendronate and risedronate, for osteoporosis. However, it seems



Figure 6. 62-year-old man on bisphosphonate therapy for osseous metastases. Postoperative radiograph. Reduced subtrochanteric femur fracture, bridged by a Stryker Gamma 11 x 40 nail that has been locked with a hip screw. Cortical thickening and characteristic ridge at the lateral aspect of the simple, transverse fracture are demonstrated (arrow).

reasonable that this type of insufficiency fracture could be seen in men taking bisphosphonates for other clinical indications such as for decreasing the complications of lytic metastases. If these fractures are the result of a class effect of the bisphosphonate medications, this pattern would be seen with intravenous forms as well, such as in our patient who was receiving intravenous Zometa, a third generation bisphosphonate. Other rare but serious risks including osteonecrosis of the jaw, usually preceded by trauma, infection, or surgery and musculoskeletal pain have been linked to both oral and intravenous forms of bisphosphonate medications [13]. As in a significant percentage of the patients in the reports of oral bisphosphonate-related fractures, our patient experienced pre-fracture prodromal pain, had diffuse cortical thickening of the femoral diaphyses, a focal cortical beak at the site of subsequent fracture, and a low energy mechanism of fracture [6].

We believe it is important to raise awareness of the potential for insufficiency fractures in patients on long term, high dose, or IV bisphosphonates. There is clearly a need to find a balance between the important benefit of these medications in patients with osteoporosis, lytic metastases, and other conditions with increased fracture



Figure 7. 62-year-old man on bisphosphonate therapy for osseous metastases. Subtrochanteric femur fracture 6 weeks after fixation. Calcified callus is present at the fracture site (arrow).

risk with the possibility of osteoclast over-suppression incapacitating the normal remodeling response to microscopic damage and resulting in insufficiency fracture. Further research is needed to establish causality and determine the exact mechanism which causes this relationship whether it is indeed the accumulation of microdamage due to inadequate remodeling, a change in the elasticity/induced brittleness of the underlying bony trabeculae, or some other mechanism [14, 15]. Optimal protocols for the dosage and duration of bisphosphonate therapy and actions to take if a patient has an impending or completed insufficiency fracture while on these medications deserve additional consideration as bisphosphonates can also adversely affect fracture healing [10, 14]. Their long dwell time and prolonged suppression of osteoclast activity in the bone can effect fracture healing in some patients months or perhaps even years after discontinuation so that additional steps may be needed to promote fracture healing [10, 14, 16, 17].

Familiarity with this pattern of clinical history and imaging findings allows the opportunity to recognize the impending fracture risk in patients with insufficiency fractures related to bisphosphonate induced over-suppression of osteoclast-dependant bone remodeling. Knowledge of the potential for low-energy fractures and poor fracture healing in this patient population will facilitate better management to prevent fracture completion and promote healing.

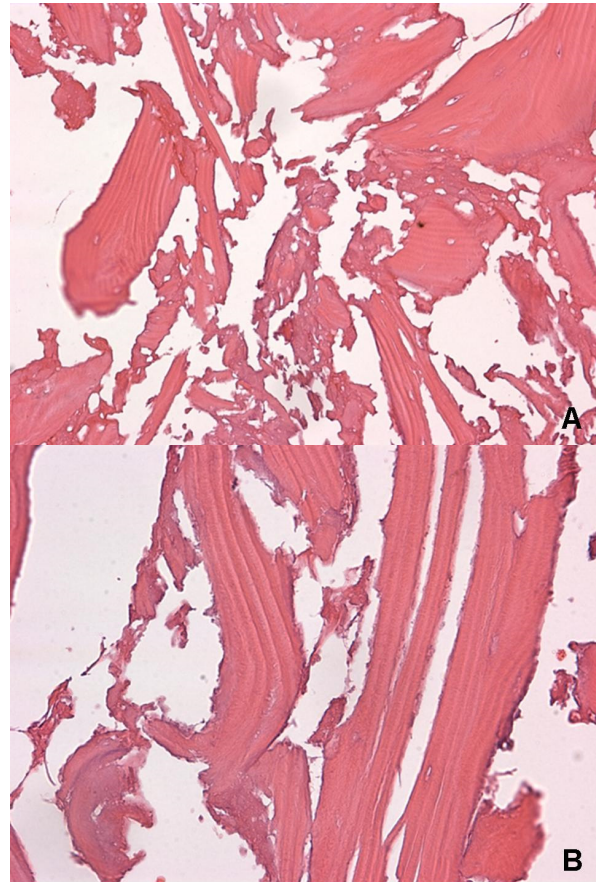


Figure 8. 62-year-old man on bisphosphonate therapy for osseous metastases. Curettage specimens from fracture site at (A) 20x, and (B) 40x demonstrate fragments of cortex. No osteoclasts are seen in any of the high powered fields reviewed for this patient. No evidence of abnormal bone remodeling or tumor was seen.

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